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## Spinal cord compression

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Spinal cord disease represents a major cause of morbidity and suffering in cancer patients. Prevention or minimization of neurologic deficits depends on an understanding of early symptoms, clinical course, and treatment options. Early diagnosis is crucial, as current treatments usually arrest the course of the disease but much less commonly restore lost neurologic function. This article will review the epidemiology, pathophysiology, symptomatology, diagnosis, and management of the causes of spinal cord dysfunction directly related to cancer. It will briefly discuss myelopathies related to paraneoplasia and treatment complications.

### **Epidural spinal cord compression**

Spinal cord or cauda equina dysfunction resulting from tumor growth in the spinal epidural space is commonly referred to as epidural spinal cord compression (ESCC). In some ways, spinal epidural metastasis (SEM) may be a better term, as it encompasses the phenomena of root, cauda equina, and minor degrees of thecal sac compression. SEM/ESCC is the most common cause of spinal cord dysfunction in cancer patients, and will receive the bulk of attention in this article.

### **Epidemiology**

Although careful, contemporary population-based studies are unavailable, the best evidence suggests that 5% of patients dying of cancer have suffered ESCC [1]. With more than 500,000 Americans succumbing to cancer yearly, there are likely to be more than 25,000 cases of ESCC yearly in the United States.

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Virtually any systemic cancer has the capacity to metastasize to the spinal column, and it is not surprising that ESCC has been reported with every major type of systemic cancer. There is a clear and strong correlation between the likelihood of systemic tumors to metastasize to the spine and the chances of developing SEM. Consequently, the incidence of SEM with a given tumor is a joint function of the incidence of that tumor and the frequency of bony spinal involvement seen in that tumor. In most adult contemporary series, prostate cancer, breast cancer, and lung cancer each are responsible for 15–20% of ESCC cases [2–4]. Non-Hodgkin's lymphoma, multiple myeloma, and kidney cancer typically each account for an additional 5–10%. Colorectal cancer, tumors of unknown primary (most of which emanate from unrecognized lung or gastrointestinal primary tumors), and sarcomas are the other common causes. Correspondingly, 90% of autopsied patients with prostate cancer have vertebral metastases, as do 74% with breast cancer, 45% with lung cancer, 29% with lymphoma or kidney cancer, and 25% with gastrointestinal cancers [5]. Children rarely develop most of the above cancers, and it comes as no surprise that the most common causes of ESCC in children differ dramatically from adults. In the pediatric population, sarcomas (especially Ewing's), germ cell tumors, and Hodgkin's disease are the most common offenders [6].

Although most cases of ESCC develop in patients who are known to have cancer, 20% of all cases arise as the initial manifestation of cancer [4]. Breast and prostate cancer are extremely unlikely to present in this fashion. In contrast, this is a common presentation of lung cancer, which accounts for 30% of cases in which ESCC is the initial manifestation of malignancy. Cancer of unknown primary, non-Hodgkin's lymphoma, and myeloma are other tumors that frequently manifest as ESCC.

### **Pathophysiology**

Most cases of SEM develop as an outgrowth of metastasis to the spinal column, which eventually invades the epidural space. The forces that result in bony spinal metastasis are incompletely understood. For many years it was thought that tumor usually accessed the vertebrae through the valveless venous system known as Batson's plexus, which drains both the vertebrae and skull and anastomoses with veins draining the breasts, thoracic, abdominal, and pelvic organs. More recently, experimental models have emphasized the role of arterial seeding of the vertebrae with tumor [7]. A less common mechanism for producing ESCC is ingrowth of tumor from the paraspinal region through the vertebral neuroforamen to compromise the intraspinal contents. Lymphomas are among the more common tumors to produce ESCC through this route [8]. Finally, tumors may rarely metastasize directly to the epidural space to produce ESCC.

Animal models of ESCC suggest that impingement of the epidural venous plexus results in venous hypertension and vasogenic edema in the

spinal cord. The salutary effects of corticosteroids are consistent with a role for vasogenic edema [9]. Direct pressure from the tumor on the spinal cord may also contribute. Without successful treatment, spinal cord infarction will eventually occur.

## **Clinical features**

### *Localization*

Spinal epidural metastases are not eventually distributed throughout the spine. Sixty percent arise in the thoracic spine, and another 30% in the lumbosacral region. These figures are proportionate to the volume of bone in each of these spinal regions. The natural kyphosis of the thoracic spine and the relatively narrow anteroposterior diameter of the thoracic spinal canal further contribute to the likelihood of developing symptomatic ESCC once epidural tumor has arisen in this region.

### *Pain*

The almost inevitable involvement of bone with tumor ensures that pain is a ubiquitous concomitant of ESCC. Pain is present in 83–95% of patients by the time of diagnosis, and has been present for a median of weeks (often much longer) [1,10,11]. Initially, the pain is localized, and typically increases in intensity with passing weeks. It may be worse with recumbency, a feature attributed to distension of the epidural venous plexus. Over time it may take on a radicular quality as well, particularly when the lumbosacral spine is involved. Thoracic epidural lesions sometimes produce bilateral, gripping girdle discomfort.

### *Motor deficits*

Weakness is the most obvious and problematic manifestation of ESCC. Unfortunately, weakness is present in 60–85% of patients at the time of diagnosis [10,12]. Moreover, two-thirds of patients with ESCC are non-ambulatory when diagnosed [13,14]. Pretreatment neurologic status is by far the most important predictor of posttreatment function, emphasizing the need for diagnosis before weakness has ensued [15,16].

When ESCC arises at or above the level of the conus, weakness is of the upper motor neuron type and is usually symmetric. The iliopsoas muscles are often preferentially affected. Weakness is most severe with thoracic ESCC [10].

### *Sensory deficits*

Patients tend to be less aware of sensory deficits than they are of weakness. Sensory deficits are slightly less common than weakness but are detectable in

the majority of patients [17]. Spinal sensory levels are usually one to five segments below the anatomic level of cord compression; radicular sensory or reflex loss is a more reliable localizer. One study suggested that root pain and sensory loss were more common with lumbosacral SEM, whereas back pain with bilateral leg weakness was typical of thoracic SEM [10]. Lhermitte's phenomenon, characterized by paresthesias in the back and extremities with neck flexion, can be seen with cervical or thoracic ESCC but may also be seen in noncompressive myelopathies related to chemotherapy or radiation.

#### *Bowel and bladder dysfunction*

Bowel and bladder disturbances tend to be a late occurrence in the development of ESCC, paralleling the degree of weakness. However, given the advanced state at which ESCC is often diagnosed, about half of ESCC patients are catheter dependent at diagnosis. The patient with an isolated difficulty with micturition or defecation is unlikely to have ESCC. Urinary retention is the most common problem associated with ESCC.

#### *Other unusual features*

Isolated gait ataxia has occasionally been reported with ESCC. Although sensory loss can produce ataxia, gait ataxia in its absence implicates disruption of spinocerebellar pathways [18].

### **Diagnosis**

Confirmation of clinically suspected ESCC depends on radiologic demonstration of thecal sac compression (Fig. 1). Ultimately this generally requires either magnetic resonance imaging (MRI) or myelography. However, several other types of studies are occasionally useful and will be discussed as well.

It is reasonable to ask, when ESCC is strongly suspected clinically and radiotherapy is planned, why radiographic confirmation is mandatory. Studies comparing radiation ports based on clinical examination and plain radiographs versus ports based on results of myelogram indicated that ports constructed without myelogram were inadequate to cover all epidural disease in 26–59% of ESCC cases [19,20]. More recently, Colletti and colleagues demonstrated that MRI altered planned treatment in >40% of cancer patients with suspected metastatic spine disease [21]. Thus, it seems inarguable that optimal treatment planning requires definitive imaging of the epidural space and thecal sac with myelogram or MRI.

#### *Plain radiographs*

Prior to the widespread availability of MRI, definitive diagnosis of ESCC mandated myelography, an invasive test uncomfortable for the patient and



Fig. 1. Epidural spinal cord compression. MRI [T2 (A) and postcontrast T1 (B)] of a 61-year-old male with hormone-refractory prostate cancer who presented with 1 month of neck and mid back pain. Neuroimaging demonstrated epidural disease at C2 and C3 and T4 and T5 with cord compression. Neurologic exam was normal except for mild hyperreflexia in the lower extremities. He was treated with 3000 cGy in 10 fractions to C1–C5 and T1–T6 with improvement in his symptoms.

occasionally contraindicated. Consequently, there was a considerable emphasis in trying to determine whether some patients were at such low risk that they did not require myelography. Plain radiographs were found to have certain uses but major limitations. Plain films were falsely negative in 10–17% of cases [1,11]. Reasons include the need for >50% of bone to be destroyed before plain radiography turns positive, the fact that paraspinous masses invading the neural foramen may not produce X-ray changes, and the fact that the multiplicity of bony metastases as seen in some common tumor like breast and prostate may confuse the picture. Moreover,



Fig. 1 (continued)

plain radiography can only show bony changes and cannot address the question of soft tissue impingement on the thecal sac or spinal cord. One study in cancer patients with back pain and radiculopathy found that major vertebral body collapse or pedicle erosion at the level of radiculopathy predicted a 75% chance of epidural disease at that level [22]. However, a recent large prospective study including both clinical and radiographic features in cancer patients suspected of having SEM found that plain radiographs did not have adequate predictive value to warrant their routine use [23].

#### *Radionuclide bone scanning*

Radionuclide bone scanning depends on increased blood flow and new bone formation to demonstrate bone metastases. Bone scanning is more sensitive than plain radiography although less sensitive than MRI for

demonstrating bone metastases. Like plain radiography, bone scans cannot identify whether epidural tumor is present. Bone scans are not useful when metastases do not produce new bone formation or increased blood flow, a situation commonly found in multiple myeloma. Bone scanning is not commonly utilized at present in the assessment of ESCC, although one retrospective study suggested that cancer patients with back pain but negative bone scans and plain radiographs had a very low incidence of ESCC and could probably forgo further radiographic evaluation [24].

### *Myelography*

Prior to the advent of MRI, myelogram was the sole means of establishing the diagnosis of ESCC. Myelography carries a small risk of exacerbating a neurologic deficit due to pressure shifts in the event of complete spinal subarachnoid block (“spinal coning”). It is also contraindicated in the presence of brain masses, thrombocytopenia, or coagulopathy. In the absence of a high-grade block, it permitted screening of the entire spinal column for epidural deposits. CT scanning at the level of SEM provided further anatomic detail, and sometimes showed passage of dye rostral to the epidural lesion that could not be seen on plain radiography; in the event of a complete block, a second spinal puncture rostral to the block was performed to delineate the complete extent of the lesion.

### *MRI*

T1- and T2-weighted MR images are generally satisfactory to screen for abnormalities in the bone and epidural space suggestive of SEM. Gadolinium administration may be helpful, as most tumors show postcontrast enhancement. Furthermore, the resolution of contrast enhancement following treatment suggests that intervention has been successful. Typically radiologists perform scans in the sagittal plane, with selected axial images through regions of interest identified on the sagittal images.

MRI offers several obvious advantages to myelography in terms of imaging SEM. It is noninvasive and images the desired spinal segment(s) irrespective of spinal block. It demonstrates bone lesions without epidural components, intramedullary metastases, and sometimes leptomeningeal tumor deposits as well. It has none of myelography’s contraindications, although there are some patients who cannot have MRIs. Several studies dating back more than a decade demonstrated that spinal MR was as sensitive as myelogram for identifying SEM [25–28]. Technical advances in MRI, as well as its incontrovertible advantages in imaging bone and spinal cord make further comparative studies unlikely, although myelography may occasionally demonstrate a laterally situated epidural lesion missed by MRI.

One potential drawback to MRI is that it is not necessarily routine to image the entire spine. Commonly, only the spinal segment suspected of

harboring SEM is scanned. The shortcoming of this approach is that multiple SEMs are found in one-third of patients. If only the symptomatic region is scanned, secondary deposits may be missed. Although the question of whether incidentally detected SEMs should be treated has not been definitively answered, radiation oncologists typically include them in treatment ports, and their presence unquestionably affects surgical decision making. Consequently, many authorities recommend either imaging the entire spine cord [11,29–31] or at least the thoracic and lumbar spine in addition to the symptomatic region; asymptomatic epidural deposits are rarely found in the cervical spine [32].

## **Treatment**

### *General supportive measures*

As indicated above, pain is the rule with ESCC and is often severe, limiting the patient functionally and frequently curtailing the examination of strength and gait. Although nonsteroidal antiinflammatory agents may provide adequate pain control, patients usually require opiates for adequate pain relief. Opiates, inactivity related to pain or neurologic deficit, and autonomic spinal dysfunction may all contribute to constipation, and valsalva maneuvers frequently exacerbate pain, so an aggressive bowel regimen should be instituted when diagnosis is suspected. The use of spinal braces is sometimes recommended. However, these devices are often quite uncomfortable, and even without them patients learn quite quickly what they can and must not do to avoid pain. Thus, their use may be limited to patients with true spinal instability.

Corticosteroids form another important part of supportive care in the patient with ESCC. They have salutary effects on pain related to bone metastases and compression of neural structures. Moreover, they have been demonstrated to improve the clinical outcome. This observation was initially made anecdotally in cancer patients with ESCC and was then confirmed in laboratory rodent models [9,33–36]. More recently, a randomized controlled trial of corticosteroids (dexamethasone 96 mg daily) versus no corticosteroids in patients undergoing radiotherapy for ESCC from solid tumors found that a significantly higher percentage of patients receiving corticosteroids were still ambulatory at long-term follow-up [37]. Because of relatively low mineralocorticoid activity, cost, and tradition, dexamethasone is the most commonly utilized agent. Although one study demonstrated no benefit from an initial bolus of 100 mg dexamethasone at diagnosis when compared to a bolus of 10 mg [38], no prospective study has addressed the optimal dose and schedule in patients with ESCC. Thus, daily dosages ranging from 16 to 96 mg daily in divided doses have their advocates. One retrospective comparison of consecutive series of patients treated at a single hospital with 96 or 16 mg as the initial daily dose identified a substantially higher

incidence of side effects in the high-dose group with no difference in efficacy [39]. In the absence of prospective randomized data, initial doses anywhere within this range are justifiable. Given the rapidity with which myopathy and other steroid-associated complications can arise, the importance of tapering steroids rapidly as tolerated (eg, if starting with 96 mg daily, halving the dose every 3 days) cannot be overstated. Patients with relative corticosteroid contraindications who have small epidural deposits that are not producing significant neurologic deficits can safely initiate treatment without corticosteroids [40].

### *Specific antineoplastic therapies*

#### *Radiation therapy*

Radiation therapy is the preferred treatment for most patients with ESCC. Once the anatomic limits of the epidural tumor have been identified, radiation oncologists specify treatment fields that extend one to two vertebral bodies above and below these limits and encompass the lateral dimensions of the SEM. To minimize the harmful effects of radiation on normal tissues, radiation is usually fractionated into small doses administered over a few days to weeks. The optimal dose-fractionation scheme for treating ESCC is unknown. One randomized trial looking at different dose-fractionation regimens for bone metastases in general did not identify any substantial difference between schedules ranging from 300 centigray (cGy)  $\times$  5 fractions to 270 cGy  $\times$  15 fractions, although reanalysis suggested that increased number of fractions was associated with improved pain control [41]. Conversely, large single fractions of radiation have been used for palliation of bone metastases without ESCC [42]. Recently, Maranzano et al have reported that the delivery of two fractions of 800 cGy 1 week apart in ESCC patients with poor neurologic prognosis is safe and apparently as efficacious as more conventional schedules; this finding requires further evaluation and confirmation [43,44]. Most radiation oncologists adhere to more standard schedules of 2500–3600 cGy in 10–15 fractions.

Radiation therapy for SEM generally produces minimal side effects. When large portions of the gastrointestinal tract are included in treatment fields, mucositis with dysphagia or diarrhea may ensue. The spinal column contains a substantial fraction of blood cell precursors, and patients who have had radiation to much of their spine may develop cytopenias. Significant fatigue and nausea are uncommon with standard treatment schedules.

Radiation therapy is efficacious in most cases in terms of preventing further tumor growth and neurologic damage. As a rule, radiotherapy ameliorates the pain of ESCC. Neurologic outcome following radiotherapy depends on three factors. In order of decreasing importance, these are (1) the degree of functional limitation when radiotherapy is instituted, (2) the tumor type, and (3) the extent of subarachnoid impingement. The importance of pretreatment neurologic status is reflected in the finding that

radiotherapy preserved the ability to ambulate in 80 to 100% of patients treated in several series who had treatment instituted while still ambulatory [1,12,16,40,45]. Approximately one-third of patients who are nonambulatory but not paraplegic prior to treatment onset will regain the ability to walk, as will 2–6% of paraplegic patients.

The importance of tumor type in determining treatment outcome is intuitive: some tumors are simply more sensitive to radiation than others. Among the particularly radiosensitive tumors are breast, prostate, and small cell lung cancer, lymphoma, and myeloma. Melanoma and renal cell carcinoma are among the most radioresistant cancers; although such patients still get significant palliation with radiation for ESCC, the chances of major functional recovery or a long-lasting response to radiotherapy are much smaller than with the radiosensitive tumors [15,17,46,47].

It is similarly intuitive that the degree of subarachnoid block is a predictor of outcome; an epidural metastasis producing a minor impression on the thecal sac should do better than a large mass obliterating the subarachnoid space, encircling and deforming the spinal cord. This has indeed been confirmed [48,49], although it is a far weaker prognostic factor than the first two.

The radiographic response of SEMs to radiation therapy has not been carefully studied, particularly in the era of MRI. In one series of patients undergoing repeat myelography for various reasons 20 to 170 days after initiation of radiotherapy, 47% had shrinkage of the SEM, 37% stable disease, and 16% progression [48].

The median survival in patients undergoing radiotherapy for ESCC varies between 3 and 6 months according to the historical series. Survival rates are higher in patients who are ambulatory either before or after radiation [15,47]. Patients with radiosensitive tumors and a single spinal metastasis do best, while patients with lung cancer, multiple vertebral metastases, or visceral or brain metastases have shorter survival [32,50–52]. From the standpoint of neurologic prognosis, about 10% of patients eventually experience local recurrence [53,54]. Risk of recurrence increases with length of survival, as one-half of 2-year survivors and nearly all 3-year survivors will develop recurrence [12,17,31]. Approximately one-half of patients surviving 1 year are still ambulatory at that time.

## **Surgery**

### *Laminectomy*

Prior to the demonstration that radiotherapy effectively palliated many patients with ESCC, the standard initial approach to newly diagnosed ESCC was decompressive laminectomy with debulking of whatever epidural was easily accessible through this posterior approach. However, laminectomy often created the problem of further destabilizing the spinal column.

A popular model of spinal stability divided the spinal column into three segments: the anterior vertebral body, posterior vertebral body, and spinal arch. Preservation of at least two of the segments is held necessary to maintain stability. As SEM usually arises from the vertebral body, laminectomy potentially weakens a spinal segment contributing importantly to stability. A comparison of retrospective case series using laminectomy with or without radiotherapy to series utilizing radiotherapy alone showed no advantage in the surgical group [13]. At present, laminectomy is performed primarily in patients in whom the bulk of epidural tumor is posteriorly located.

### *More extensive procedures*

The recognition that posterior approaches did not allow for adequate exposure to debulk epidural tumor, decompress the spinal cord, and stabilize the spinal column led to development of vertebral corpectomy as an alternative. This technique, pioneered and refined by Siegal, Harrington, and Sundaresan among others, utilized an anterior or anterolateral approach to get into the affected vertebral body and core out the tumor (including accessible components in the epidural space). At this point the spine generally requires stabilization. Either bone or methylmethacrylate can serve this purpose. Adjuvant radiotherapy must wait at least 6 weeks if bone is used so that bony union can occur, whereas the delay need not exceed 1 week with methylmethacrylate. Patients are mobilized within a few days of surgery [55–57].

Evaluation of the results of vertebral corpectomy is difficult, as no randomized trial comparing outcomes to those of radiotherapy has been completed. Moreover, surgical case series are prone to selection bias favoring the inclusion of relatively healthy patients. Nonetheless, the results of reported surgical series are impressive. For example, in one of the largest series, Sundaresan operated on 110 patients, 47 of whom had failed prior radiotherapy. Preoperatively, 44% were nonambulatory. Eighty-two percent of patients were improved, with a median survival of 16 months and 46% 2-year survival [57].

Complications of aggressive resection and spinal stabilization are very common. In Sundaresan's series, 48% of patients experienced surgical complications. Common complications included wound breakdown, hemorrhage, stabilization failure, and infection. One-month mortality was 10%. Complications were most likely in patients older than 65 and in those who were paraparetic or who had prior radiotherapy.

Pending results of randomized controlled trials comparing surgery to radiotherapy (one of which is underway in the United States), no definitive guidelines regarding the merits of the two approaches can be made. It is reasonable to consider vertebral corpectomy as first-line treatment in patients with spinal instability, SEMs arising from radioresistant primary tumors

when extraspinal disease is limited or controllable, deterioration during or recurrence following radiotherapy.

## **Chemotherapy**

Chemotherapy is a reasonable treatment option for ESCC when the underlying tumor is likely to be chemosensitive. Unfortunately, many of the common causes of ESCC are resistant to chemotherapy either from the start or by the time ESCC has arisen. Nonetheless, chemotherapy has been successfully used for both Hodgkin's and non-Hodgkin's lymphoma [58,59], as well as breast cancer, germ cell tumors, and neuroblastoma [60–62]. Hormonal manipulation has also been successfully employed in hormone-naïve patients with ESCC from breast or prostate cancer [63,64]. More commonly, given the uncertain benefits, the addition of hormonal therapy or institution or change in cytotoxic chemotherapy follows radiotherapy.

### *Novel approaches*

The delivery of extremely precise radiation therapy in a single fraction is known as stereotactic radiosurgery. The utility of stereotactic radiotherapy for brain metastases is unquestioned. Recently, there have been attempts to modify linear accelerators and localization devices to deliver stereotactic radiation to spinal metastases [65]. Whether this technique will be able to deliver biologically effective doses of radiation to tumor that may be contiguous with and encircle the spinal cord without producing radiation myelopathy remains to be determined.

### *Recurrent ESCC*

As mentioned earlier, about 10% of patients will eventually develop local recurrence of SEM. Little attention has been paid to this population. Most such patients have previously received radiotherapy, and few have reliably effective chemotherapy options at this stage of their illness. Aggressive spinal surgery should be considered in these patients, although many have advanced visceral disease limiting their life expectancy to a few months or widespread spinal metastases detracting from surgical feasibility. One retrospective study of 51 patients undergoing a second course of spinal radiation for ESCC found that reirradiation was highly successful in preserving neurologic function and rarely resulted in radiation myelopathy (whether because patients did not live long enough or conventional estimates of spinal cord radiation tolerance are overly conservative) [66].

### *Intramedullary spinal cord metastases*

Parenchymal metastasis to the spinal cord, also known as intramedullary spinal cord metastasis (ISCM), was infrequently recognized during the

myelography era. During that time, only masses producing substantial spinal cord swelling could be detected. With the advent of MRI, ISCM has been more readily detected, with an incidence about 1/16th that of SEM [67]. Like SEM, ISCM can produce myelopathy and back pain. Pain tends to be a little less ubiquitous and severe than with SEM. Another feature that should suggest ISCM is a Brown-Sequard syndrome, or a strong asymmetry in a myelopathy. This is seen in almost half of patients with ISCM and only 3% of patients with ESCC [67]. ISCMs are most often single and can arise in any cord segment; a majority of patients with ISCM have brain metastases, and one-quarter have concomitant leptomeningeal carcinomatosis. Lung cancer accounts for a majority of cases, with melanoma, lymphoma, renal cell, and breast carcinoma other common culprits [67–69]. MR scan readily differentiates ISCM from SEM, revealing parenchymal circumscribed contrast enhancement with a larger surrounding area of T2 signal indicative of edema (Fig. 2). Treatment of ISCM generally consists of fractionated radiotherapy, which usually arrests tumor growth and prevents further neurologic deficit [67]. Surgery is rarely indicated, given the inherent risks of operating on the spinal cord and the usual state of advanced cancer elsewhere in these patients.



Fig. 2. Intramedullary spinal cord metastasis. Sagittal (A) and axial (B) postgadolinium T1-weighted MR scans. This 55 year old with a history of small-cell lung cancer presenting with brain metastases 18 months earlier developed trouble walking, burning in both legs, but no back pain. Exam revealed pyramidal-type left leg weakness and proprioceptive loss. The MR scan reveals abnormal signal and swelling within the conus from T10 to the tip of the conus. Her symptoms improved with radiotherapy.



Fig. 2 (continued)

### *Vertebral metastases without SEMIESCC*

Vertebral metastases without epidural extension commonly produce back pain in cancer patients. The neurologist must recognize that the absence of radiculopathy or myelopathy does not ensure that epidural disease is not present; in fact, huge epidural metastases compressing the spinal cord, if slowly growing, may produce no symptom apart from back pain. The risk of epidural disease in patients with cancer and back pain who come to myelogram or MRI, even in the absence of radiculopathy or myelopathy, is approximately 30% [23,70,71].

### *Radiation myelopathy*

Radiation myelopathy is generally divided into four subtypes:

1. Acute, complete myelopathy (occurring over hours and presumably vascular in origin).
2. A pure lower motor neuron form
3. Acute transient radiation myelopathy, manifesting as Lhermitte's phenomenon
4. Chronic progressive radiation myelopathy

Numbers 1 and 2 are quite rare, while 3 is of little significance as it does not predispose to chronic or severe complications. Thus, for the most part, when clinicians speak of radiation myelopathy, they are referring to 4.

Chronic progressive radiation myelopathy is a rarely seen complication today. Every type of body tissue has its own tolerance to radiotherapy, and spinal cord is one of the most sensitive tissues. Radiation tolerance depends on several factors, including the total dose of radiation received, the number of fractions over which it was delivered, the number of days, and the length of spinal cord irradiated. Increasing total dosage, large fraction size or smaller fraction number, shorter treatment times, and longer spinal cord segments all increase the risk of radiation myelopathy. Radiation oncologists strive to avoid producing radiation myelopathy, and generally have restricted spinal cord dose to figures with a  $\leq 5\%$  chance of inducing this complication. The dosing schedule with a 5% risk has been estimated to be 4200–4500 cGy in 25 fractions [72,73]. However, current evidence suggests this may be an overly conservative estimate, and that the true risk with this schedule is 0.2%, whereas 6000 cGy in 30 fractions carries a 5% risk of radiation myelopathy [73]. Although chronic progressive radiation myelopathy can occur any time after radiotherapy, median latency is 1 or 2 years.

The symptoms of radiation myelopathy may include ascending weakness and clumsiness, diminished sensation, temperature discrimination, and proprioception. Commonly the symptoms have a hemicord localization, so that weakness and impaired temperature discrimination may be crossed. Symptoms often progress over months, and may result in complete transverse myelopathy or lesser degrees of involvement. MR imaging shows parenchymal T2 hyperintensity consistent with edema, sometimes with focal contrast enhancement indicative of blood-spinal cord barrier breakdown. There are no proven effective treatments; corticosteroids may be of transient benefit, and anticoagulation has anecdotally been reported useful [74,75].

### **Leptomeningeal disease**

Leptomeningeal carcinomatosis (Fig. 3), discussed elsewhere in this volume, frequently involves the spinal cord and cauda equina, occasionally in the absence of intracranial disease. The clinical manifestations almost always are of multiple radiculopathies and not myelopathy, although leptomeningeal tumor and ISCM may coexist.

### **Myelopathy related to chemotherapy**

Cisplatin and very high doses of BCNU and fludarabine have been reported to produce myelopathy following intravenous administration; these represent exceedingly rare events. Transverse myelopathy has been convincingly associated with intrathecal injections of various chemotherapies, most commonly methotrexate but also cytarabine and thiotepa. Typically, onset of back or leg pain, paraplegia, and sensory loss begin within hours to a few days of treatment. The pathogenesis is unknown, as is

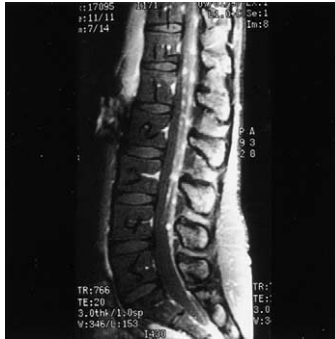


Fig. 3. Leptomeningeal metastases. This 34 year old had a 3-year history of melanoma and an 18-month history of brain metastases. She then presented with sciatic-type leg pain followed by constipation and patchy sensory loss from her chest to her thighs. She manifested a markedly positive straight leg raise, mild leg weakness, and diminished deep tendon reflexes in her legs. The postgadolinium MR scan demonstrates numerous small leptomeningeal enhancing nodules.

optimal treatment; some patients improve over time. Anthracycline antibiotics (such as Adriamycin and mitoxantrone) and vinca alkaloids reliably produce myelopathy when injected intrathecally, and are thus never administered via this route [76].

### Paraneoplastic myelopathy

Paraneoplastic syndromes uncommonly affect the spinal cord, and rarely affect it in isolation. By far the most common syndrome to affect the cord is paraneoplastic encephalomyelitis. This entity is associated with anti-Hu antineuronal antibodies, and may manifest as limbic encephalitis, brainstem encephalitis, myelitis, subacute sensory neuronopathy, or combinations thereof. The usual cause is small cell lung cancer [77].

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